Rapid Drink Challenge in high-resolution manometry: an adjunctive test for detection of esophageal motility disorders

Ang, D ; Hollenstein, M ; Misselwitz, B ; Knowles, K ; Wright, J ; Tucker, E ; Sweis, R ; Fox, M

Abstract: BACKGROUND/AIMS The Chicago Classification for diagnosis of esophageal motility disorders by high-resolution manometry (HRM) is based on single water swallows (SWS). Emerging data suggest that a "Rapid Drink Challenge" (RDC) increases sensitivity for motility disorders. This study establishes normal values and diagnostic thresholds for RDC in clinical practice. METHODS Two cohort studies were performed in patients with dysphagia or reflux symptoms (development and validation sets). Healthy subjects and patient controls provided reference values. Ten SWS and two 200-mL RDC were performed. Primary diagnosis for SWS was established by the Chicago Classification. Abnormal RDC was defined by impaired esophagogastric junction (EGJ) function (elevated integrated relaxation pressure during RDC [IRP-RDC]); incomplete inhibition of contractility during and ineffective contraction after RDC. Diagnostic thresholds identified in the development set were prospectively tested in the validation set. RESULTS Normal values were determined in healthy (n=95; age 37.8 ± 12) and patient controls (n=44; age 46.4 ± 15). Development and validation sets included 178 (54 ± 17 years) and 226 (53 ± 16 years) patients, respectively. Integrated relaxation pressure during RDC was higher for SWS than RDC in all groups (overall P<.001), except achalasia. Rapid Drink Challenge suppressed contractility, except in achalasia type III, spasm, and hypercontractile motility disorders (P<.001). An effective after-contraction was present more often in health than disease (P<.001). Optimal diagnostic thresholds identified in the development set (IRP-RDC 12 mmHg achalasia, IRP-RDC 8mmHg "all cause" EGJ dysfunction), were confirmed in the validation set (both, sensitivity 85%, specificity >95%). CONCLUSIONS Rapid Drink Challenge contributes clinically relevant information to routine HRM studies, especially in patients with EGJ dysfunction.

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ORIGINAL ARTICLE

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Rapid Drink Challenge in high-resolution manometry: an adjunctive test for detection of esophageal motility disorders

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Abstract

Background/Aims: The Chicago Classification for diagnosis of esophageal motility disorders by high-resolution manometry (HRM) is based on single water swallows (SWS). Emerging data suggest that a "Rapid Drink Challenge" (RDC) increases sensitivity for motility disorders. This study establishes normal values and diagnostic thresholds for RDC in clinical practice.

Methods: Two cohort studies were performed in patients with dysphagia or reflux symptoms (development and validation sets). Healthy subjects and patient controls provided reference values. Ten SWS and two 200-mL RDC were performed. Primary diagnosis for SWS was established by the Chicago Classification. Abnormal RDC was defined by impaired esophagogastric junction (EGJ) function (elevated integrated relaxation pressure during RDC [IRP-RDC]); incomplete inhibition of contractility during and ineffective contraction after RDC. Diagnostic thresholds identified in the development set were prospectively tested in the validation set.

Results: Normal values were determined in healthy (n=95; age 37.8 ± 12) and patient controls (n=44; age 46.4 ± 15). Development and validation sets included 178 (54 ± 17 years) and 226 (53 ± 16 years) patients, respectively. Integrated relaxation pressure during RDC was higher for SWS than RDC in all groups (overall $P<.001$), except achalasia. Rapid Drink Challenge suppressed contractility, except in achalasia type III, spasm, and hypercontractile motility disorders ($P<.001$). An effective after-contraction was present more often in health than disease ($P<.001$). Optimal diagnostic thresholds identified in the development set (IRP-RDC ≥12 mmHg achalasia, IRP-RDC ≥ 8mmHg "all cause" EGJ dysfunction), were confirmed in the validation set (both, sensitivity ~85%, specificity >95%).

Conclusions: Rapid Drink Challenge contributes clinically relevant information to routine HRM studies, especially in patients with EGJ dysfunction.

KEYWORDS

diagnostic classification, esophageal motility disorders, high-resolution manometry, multiple water swallows, prospective cohort study, Rapid Drink Challenge

1 | INTRODUCTION

Patients with persistent dysphagia or reflux symptoms without diagnostic findings on upper gastrointestinal endoscopy and that do not respond to empirical medical treatment are referred for physiologic investigations.[1] High-resolution manometry (HRM) with pressure data presented as topographic ("Clouse") plots delivers a continuous assessment of esophageal function from the pharynx to the stomach.[1] The Chicago Classification (CC) provides a diagnosis of esophageal motility disorders based on objective HRM metrics that has been validated against tests of esophageal function and clinical outcome.[2–6] Nevertheless, HRM studies have important limitations. Firstly, the sensitivity of the classification system for diagnosis of certain disorders, including achalasia type I and esophago-gastric junction (EGJ) outlet obstruction is suboptimal.[7,8] Secondly, the specificity and clinical relevance of other diagnoses, including hypercontractile ("jackhammer") esophagus and ineffective esophageal motility (IEM) is debated.[9,10] Thirdly, many patients who complete HRM do not receive a diagnosis that explains their symptoms.[11,12] One reason for these limitations is that routine HRM studies utilize single water swallows (5–10 mL SWS) in the supine position. This approach is not representative of normal drinking during which many patients are symptomatic.

The Rapid Drink Challenge (RDC), also referred to as the Multiple Water Swallow test,[13] involves ingestion of a specified volume of water in a series of swallows as in normal drinking behavior.[1,14] Rapid Drink Challenge enhances central and peripheral deglutitive inhibition resulting in profound suppression of contractions in the esophageal body and complete relaxation of the lower esophageal sphincter (LES). The final swallow may be followed by an augmented peristaltic and LES after-contraction (Fig. 1). Thus, an abnormal response involves either incomplete inhibition of EGJ or peristaltic contractility during swallows and/or an abnormal contraction after the swallows. Rapid Drink Challenge can be compared to the "Multiple Rapid Swallow (MRS)" test for which a small volume of water (5–10 mL) is taken in four to six rapid swallows;[15,16] however, a larger amount of water (200 mL) is ingested during the RDC test. Initial studies suggest that this adjunctive test may represent a clinically relevant challenge that increases the sensitivity of HRM studies for detecting esophageal motility disorders, in particular, those associated with EGJ dysfunction.[1,8,13]

To date, RDC findings have been reported from retrospective reviews of patients with esophageal motility disorders[1,8,13] with only

Key Points

- Emerging data suggest that a 200-mL Rapid Drink Challenge (RDC) test provides additional information during esophageal high-resolution manometry (HRM).
- We present normal values for RDC from healthy volunteers and patient controls and establish diagnostic thresholds for esophagogastric junction (EGJ) and peristaltic dysfunction.
- Rapid Drink Challenge is easy, quick, and cost-free to perform during routine HRM studies and appears to increase diagnostic yield for symptomatic EGJ outflow obstruction and other, clinically relevant, motility disorders.

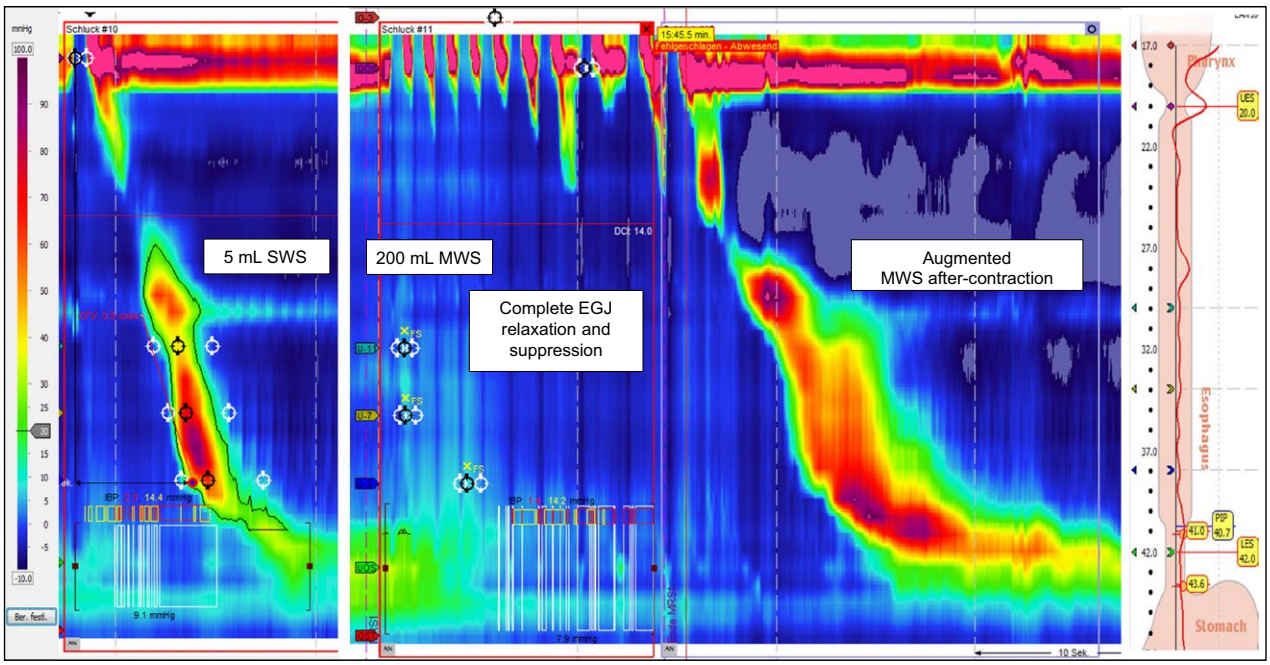

FIGURE 1 Normal single water swallows (SWS) and Rapid Drink Challenge (RDC) in a healthy subject. Complete esophago-gastric junction (EGJ) relaxation (integrated relaxation pressure during RDC [IRP-RDC] of 4 mmHg) and suppression of esophageal body contractility is present. An effective after contraction clears the esophagus following RDC. In this case, augmentation is present. RDC:SWS DCI ratio >1 (here DCI 3374:1173 = 2.9)

one of these studies by Marin and Serra[13] including both healthy volunteers (HV) and patients with esophageal motility disorders. Specific HRM pressure responses during RDC have been described in health and disease.[13] However, normal values for RDC in healthy subjects and diagnostic thresholds in patients based on objective HRM metrics have not been established.

1.1 | Aims

The objectives of this study were: (i) to establish normal values for standard HRM metrics that describe esophageal motility and function during RDC, (ii) to determine optimal diagnostic criteria based on these metrics in a "development set" of patients that included the full range of major motility disorders, and (iii) validate the performance of these criteria in an independent, prospectively collected "validation set" of patients referred for the investigation of esophageal symptoms. These findings could provide a classification system for RDC and insight into its clinical utility in routine HRM studies.

2 | METHODS

2.1 | Controls

Healthy volunteers with no gastrointestinal symptoms or clinically relevant past medical history were recruited by advertisement (reimbursement of CHF70 was available). "Patient controls" included individuals referred for investigation of upper gastrointestinal symptoms but with a normal esophageal HRM study based on Chicago Classification v3.0 and normal 24-hour pH studies.

2.2 | Patients

The development set included all patients with major motility disorders identified over the first 3 years of the study *plus* all patients investigated in the final year of recruitment in Nottingham. The prospective validation set included consecutive patients referred for esophageal studies over the full study period in Zürich. Classification of major and minor esophageal motility disorders was based on the Chicago Classification version 3.0.[2]

Development and validation sets included patients referred for physiological evaluation of esophageal function at Nottingham University Hospital, UK (January 2010–December 2013) and University Hospital of Zürich, Switzerland (January 2013–December 2014), respectively.

Participants stopped acid suppression and any prokinetic medications 1 week prior to the study. Demographic data, symptoms, endoscopy findings, current medication, past medical and surgical history were recorded. Informed consent was obtained from all patients. All patients and controls provided permission for data to be analyzed. Studies were approved by local ethics committees and registered at ClinicalTrials.gov: NCT00482885, NCT02407938, NCT02397616.

2.3 | Data acquisition: high-resolution manometry

Participants were studied after a minimum 4-hour fast. High-resolution manometry was performed only in the upright position as many patients, especially those with major motility disorders, cannot complete RDC lying down.[11] Measurements of baseline EGJ function were obtained followed by 10 swallows of 5 mL water administered by a syringe. The patient then drank 200 mL water from a cup by multiple water swallows (RDC) without stopping. Rapid Drink Challenge was repeated after ingestion of a test meal (reported elsewhere).

All participants were asked at the beginning of the study to report any symptoms of dysphagia, chest pain, and/or regurgitation during the procedure. These were recorded contemporaneously in the electronic record.

2.4 | Data analysis: HRM

Proprietary software analyzed HRM spatiotemporal (Clouse) plots (Manoview version 3.0.1; Given Imaging, Duluth, GA, USA). All measurements were referenced to gastric pressure.

2.5 | Single water swallows (SWS)

Ten SWS were evaluated to assess esophageal motility and function. Manometric diagnosis was based on the standard 5-mL SWS according to the CC,[2] modified for use in the upright position.[17]

2.6 | Rapid Drink Challenge (RDC)

Data were broadly classified into abnormalities that occur during the swallows, and immediately after the swallows. Abnormalities during the swallow include failure of LES relaxation, pan-esophageal pressurization (PEP), and lack of inhibition of contractility.[8,13] Abnormalities immediately after the swallow include an absent/ineffective or abnormal esophageal after-contraction. Rapid Drink Challenge data were evaluated to assess EGJ and esophageal body inhibition during swallows and contraction following swallows. We used the "IRP-tool" in ManoView 3.0.1 to define integrated relaxation pressures during the rapid drink challenge (IRP-RDC) in the upright seated position. This "IRP-tool" measured e-sleeve pressure during the duration of rapid liquid ingestion with obvious artifacts removed (e.g., cough). The vigor of the RDC after-contraction was assessed by distal contractile integral (DCI).

As a starting point, based on physiological investigation and pilot clinical studies,[8,11,18] the preliminary classification of RDC findings applied normal values defined for SWS by the Chicago Classification.[2] Abnormal RDC was defined by: (i) impaired EGJ relaxation/opening, defined by "IRP-RDC" >15 mmHg during RDC and/or presence of PEP (pressurization ≥30 mmHg from the upper esophageal sphincter to the EGJ); (ii) failure to suppress peristaltic contractions (contractions measuring >3 cm using the 20 mmHg isobaric contour tool during RDC); and (iii) failure to generate an effective after-contraction (augmentation was noted). An effective after-contraction was defined

as coordinated peristalsis occurring within 30 seconds after the last swallow with DCI >450 mmHg/s/cm and <5 cm break in the 20 mmHg isobaric contour. Mean DCI from two RDC after-contractions were compared against mean DCI from 10 SWS. A DCI ratio for RDC/SWS ≥1 was regarded as an augmented response, as described for MRS.[15]

Subsequently, optimal diagnostic criteria/thresholds for HRM metrics during RDC were identified by "receiver operating characteristic" (ROC) analysis. Diagnosis based on SWS was the reference standard. Following the approach used by the CC,[6,19] diagnostic thresholds for IRP-RDC were refined using results in achalasia patients to define clinically relevant, abnormal EGJ function. The process was repeated for "all cause" EGJ dysfunction (achalasia and outlet obstruction).

2.7 | Prospective validation

The performance of diagnostic thresholds identified by the development set was tested in the validation set. Only RDC metrics that were at least "substantially" reproducible and achieved at least "good" levels of diagnostic accuracy defined by ROC were tested (see statistics for criteria).

2.8 | Statistical analysis

The primary analysis compared the prevalence of inhibitory and contractile RDC abnormalities for each esophageal motility disorder based on ten 5-mL SWS using the Chicago Classification version 3.0. Integrated relaxation pressure during RDC and DCI after RDC was compared with the same measurements from ten 5-mL SWS in patients and controls. Secondary analyses compared frequency of symptoms during SWS and RDC.

Reproducibility of objective metrics (e.g., DCI, IRP-RDC) during RDC1 and RDC2 was assessed by Bland-Altman analysis. Reproducibility of inhibitory and contractile RDC findings (categorical measurement) on repeat testing was assessed by the kappa statistic (strength of agreement: 0–0.2 ["poor"]; 0.21–0.40 ["fair"]; 0.41–0.60 ["moderate"]; 0.61–0.80 ["substantial"]; 0.81–1.00 ["almost complete-complete"]).

Patient data are reported as mean ± standard deviation (SD) or median (95% confidence intervals [CI]) as appropriate. Normal ranges are defined by the 99% CI from combined patient and healthy controls. Optimal diagnostic thresholds based on ROC findings were identified in the development set. An area under the ROC curve (AUC) 0.80–0.90 defined "good" and >0.90 "excellent" accuracy for medical tests. Sensitivity and specificity, positive and negative predictive values of these thresholds were prospectively assessed in validation set.

Inter-group differences were compared using chi-square or Fisher's exact test for categorical values and Student's *t*-test for continuous variables. Pairwise differences were analyzed with Wilcoxon signed rank test. Statistical analysis was performed using the SPSS 18.0 package for Windows (SPSS Inc., Chicago, IL, USA). All authors had access to the study data and reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Study participants

Demographic and clinical data for study groups are presented in Tables 1 and 2. Controls comprised 95 HV (N=50 [53%] male; mean age 38 ± 12 years), plus 44 patient controls without esophageal symptoms in whom HRM and pH-studies were normal (N=20 [46%] male; mean age 46 ± 15 years). The development set of 178 patients (76 [43%] male; mean age 54 ± 17 years) included 108 (represents 15% of all referrals) consecutive patients diagnosed with major motility disorders. The validation set of 226 consecutive patients (104 [46%] male; 53 ± 16 years) included 42 (19% of referrals) patients with major motility disorders.

3.2 | RDC in healthy and patient controls

No important differences in demographic characteristics and physiological measurements were present between healthy and patient controls (Tables 1 and 2) and, therefore, these data were combined for the primary analysis (N=139). Using the 99% CI, the upper limit of normal for IRP-RDC and DCI was lower for RDC than SWS (IRP-RDC 2.8 vs 5.1 mmHg, DCI 992 vs 1172 mmHg/s/cm). One control had IRP >15 mmHg with SWS; however, IRP-RDC was within normal limits during drinking. Incomplete deglutitive inhibition during RDC was seen in six (4.3%) controls. One had esophageal spasm (DL <4.5 seconds) on SWS, others completed the drink slowly with pauses between swallows (i.e., false positive). An effective after-contraction was present in 55% with augmentation observed in one-third of controls (Table 3). Two controls had a hypercontractile after-contraction on at least one occasion.

TABLE 1 Demographic data for patients and controls

	Patient: Development	Patient: Validation	Patient: Controls	Healthy Controls
Subjects (N)	178	226	44	95
Age (mean ± SD) years	54.3 ± 16.6*,**	53.1 ± 16.4*,**	46.4 ± 14.8	37.8 ± 11.9
Male: Female	76:102	104:112	20:24	50:45
Symptoms	Dysphagia 134 Reflux 44	Dysphagia 80 Reflux 111 Atypical 30 Pre-op 5	Dyspepsia 32 Cough 6 Pre-op 6	None

*P<.005 compared to patient controls.
**P<.001 compared to healthy controls.

TABLE 2 Duration of Rapid Drink Challenge (RDC) and number of swallows taken by patients and controls

	Dysphagia	Reflux	Disease controls	Healthy volunteers
RDC duration (mean ± SD)	23.1 ± 16.3**	24.5 ± 22.4*	20.1 ± 9.1	16.3 ± 8.1
No of swallows (mean ± SD)	12 ± 5	13 ± 5	13 ± 4	12 ± 5

*P<.05 compared to healthy volunteers.

**P<.01 compared to healthy volunteers.

TABLE 3 Proportion of abnormal results in validation set based on Rapid Drink Challenge in patient and control groups. Diagnostic thresholds defined for SWS by CCv3.0

		Rapid Drink Challenge (RDC)			
Diagnosis (based on SWS result)	N	Raised IRP-RDC >15 mmHg ± PEP (i.e., impaired EGJ function) (% total)	Failure of deglutitive inhibition during RDC ± spasm (% total)	Effective RDC after-contraction (% total)	Augmented DCI in RDC after-contraction (RDC:SWS >1) (% total)
Achalasia type 1	3	**2 (66.7)****	0 (0.0)	0 (0.0)	0 (0.0)
Achalasia type 2	19	**18 (94.7)*****	0 (0.0)	0 (0.0)***	0 (0.0)**
Achalasia type 3	12	**10 (83.3)*****	**3 (25.0)***	4 (33.3)	1 (8.3)
EGJ outflow obstruction	23	**6 (26.1)*****	2 (8.7)	**7 (30.4)***	6 (26.1)
Spasm/Jackhammer	17	1 (5.9)	**11 (64.7)*****	11 (64.7)	**1 (5.9)***
Aperistalsis	34	**3 (8.8)****	1 (2.9)	**1 (2.9)*****	**1 (2.9)*****
Nutcracker	10	0 (0.0)	**3 (30.0)***	8 (80.0)	3 (30.0)
Ineffective motility	60	0 (0.0)	1 (1.7)	29 (48.3)	16 (26.7)
Controls	139	0 (0.0)	6 (4.3)	77 (55.4)	46 (33.1)

*P<.05; **P<.01; ***P<.001 compared to controls PEP pan-esophageal pressurization.

Results for patient and healthy controls were combined as there was no difference between manometric findings between these two groups. The bold numbers referred to the significant results (i.e., P<0.05 compared to controls).

3.3 | RDC in controls vs patients

No significant differences occurred in the number of swallows taken during RDC for controls and patients (12[5] vs 12[4]; pNS); however, controls completed RDC more quickly (18[9] vs 23[18] seconds; P=.001). The duration of swallows and number of swallows required did not differ between patients with dysphagia or reflux symptoms (Tables 1 and 2). No control experienced symptoms during HRM studies. More patients reported symptoms during RDC than during 10 SWS (n=55 [30.9%] vs n=6 [3.4%], P<.0001), including dysphagia (n=45 [25% of total]), chest discomfort (n=12 [6.7%]), and regurgitation (n=12 [6.7%]).

3.4 | RDC in major and minor esophageal motor disorders

Comparisons of SWS and RDC metrics are presented in Tables 4 and 5. Integrated relaxation pressure during RDC was higher for SWS than RDC in controls and all patient groups (overall P<.001), except achalasia.

The frequency of RDC abnormalities in different motility disorders is presented in Table 3. Normal findings are shown in Fig. 1. Applying the standard SWS IRP >15 mmHg diagnostic threshold, impaired EGJ function was present in 30/34 (88%) patients with achalasia and 6/23 (26%) with EGJ outflow obstruction (Table 3). Conversely, three patients (9%) with aperistalsis and a normal IRP on SWS had pathological IRP-RDC indicating EGJ dysfunction during RDC (Fig. 2). This was observed also in one patient with esophageal spasm. Additionally, hypercontractile contractions and EGJ outflow obstruction were sometimes evident only on the RDC test and not on the routine SWS protocol (Fig. 3).

Failure to suppress contractions during RDC was seen in some patients with achalasia type III, spasm, and hypercontractile motility disorders (Fig. 4), but rarely in other patient groups (16/52 [31%] vs 5/126 [2%] P<.001).

An abnormal RDC after-contraction was observed in more patients with major than minor motor disorders or controls (85/108 [79%] vs 33/70 [47%] and 62/139 [44%]; P<.001). Conversely, 48% (n=29/60) of patients with ineffective motility and one with aperistalsis on SWS generated a normal RDC after-contraction (Table 3).

3.5 | Development and validation of diagnostic thresholds

Receiver operating characteristic analysis demonstrated “excellent” accuracy of IRP-RDC for diagnosis of achalasia and “all cause” EGJ dysfunction during RDC in the development set (both AUC >0.95;

TABLE 4 Comparison between IRP-RDC (integrated relaxation pressure during Rapid Drink Challenge) metrics measured during single water swallows and Rapid Drink Challenge in upright position (validation set)

	N	SWS IRP-RDC (median, 95% CI)	RDC IRP-RDC (median, 95% CI)	*P* value for comparison SWS & RDC
Achalasia type 1	3	16.8 (15.6, 24.4)***	17.0 (12.3, 24.6)***	NS
Achalasia type 2	19	21.1 (15.2, 31.8)***	24.5 (15.3, 34.3)***	NS
Achalasia type 3	12	23.4 (21.7, 28.3)***	21.8 (16.4, 25.8)***	NS
EGJ outflow obstruction	23	17.6 (14.9, 21.7) ***	9.3 (7.7, 12.2)***	<0.01
Aperistalsis	34	4.2 (2.0, 8.0)	2.7 (0.7, 21.5)*	<0.05
Spasm/Jackhammer	17	7.1 (4.6, 9.6)	2.1 (0.3, 6.5)*	<0.05
Nutcracker	10	9.9 (7.1, 22.0)	2.6 (0.0, 11.4)	<0.001
Ineffective motility	60	4.8 (3.7, 6.7)	0.98 (0.3, 2.7)	<0.001
Control subjects (median, 99% CI) HV and patient controls combined	139	4.7 (3.9, 5.6)	1.5 (0.8, 2.0)	<0.001

*P<.05, ***P<.001 for comparisons of IRP-RDC metrics with control group.

Results for patient and healthy controls were combined as there was no difference between manometric findings between these two groups.

TABLE 5 Comparison between DCI (distal contractile integral) metrics measured during SWS (single water swallows) and Rapid Drink Challenge in upright position (validation set)

	N	SWS DCI (median, 95% CI)	RDC DCI (median, 95% CI)	*P* value for comparison SWS & RDC
Achalasia type 1	3	0 (0, 604)*	0 (0, 0)***	NS
Achalasia type 2	19	757.6 (108, 1791)	0 (0, 0)***	<0.05
Achalasia type 3	12	2359 (433, 3820)**	0.0 (0, 2333)*	<0.05
EGJ outflow obstruction	23	1042 (434, 1260)	157 (0, 1636)	NS
Aperistalsis	34	0 (0, 127)***	0 (0, 0)***	NS
Spasm/Jackhammer	17	2126 (828, 4931)*	518 (141, 3206)	NS
Nutcracker	10	2860 (1452, 4735)*	1762 (199, 3980)	NS
Ineffective motility	60	372 (280, 501)**	144* (49, 325)	NS
Control subjects (median, 99% CI) HV and patient controls combined	139	1029 (827, 1231)	762 (554, 1039)	NS

*P<.05, **P<.01, ***P<.001 for comparisons of DCI metrics with control group.

Results for patient and healthy controls were combined as there was no difference between manometric findings between these two groups.

P<.001). Optimal diagnostic thresholds were in the range of 10–12 and 7–9 mmHg, respectively (Fig. 5). Failure to suppress contractility had high specificity but low sensitivity for spastic and hypercontractile motility disorders. The presence or absence of the RDC after-contraction did not distinguish patient and control groups and, therefore, this was not tested in the validation set.

In the validation set RDC IRP-RDC >12 mmHg had optimal diagnostic accuracy for achalasia. The performance of IRP-RDC >15 mmHg was similar in this set; however, IRP-RDC >12 mmHg was preferred because the higher value would have missed few cases in the development set. IRP-RDC >8 mmHg had optimal accuracy for "all cause" EGJ dysfunction (Fig. 5).

3.6 | RDC reproducibility

Reproducibility of IRP-RDC and DCI on repeated measurements was assessed (Figure S1). There was no important difference in mean IRP-RDC (mean difference = +1.0, 95% CI [0.3–1.8]) or DCI values between the first and second RDC (mean difference = +238, 95% CI [−77, 555]).

In the categorical analysis, there was a "substantial" level of reproducibility for normal/abnormal EGJ function and for success/failure of deglutitive inhibition during RDC (kappa 0.78 and 0.67, respectively). Reproducibility for the presence/absence of an effective RDC after-contraction was poor (kappa statistic 0.34).

4 | DISCUSSION

This study presents and validates standard operating procedures for the performance and analysis of the adjunctive "Rapid Drink Challenge" (RDC) during routine, clinical high-resolution manometry (HRM) studies. Normal values are presented from a large cohort of controls. Characteristic RDC findings in patients with a full range of esophageal motility disorders are described. Based on this data,

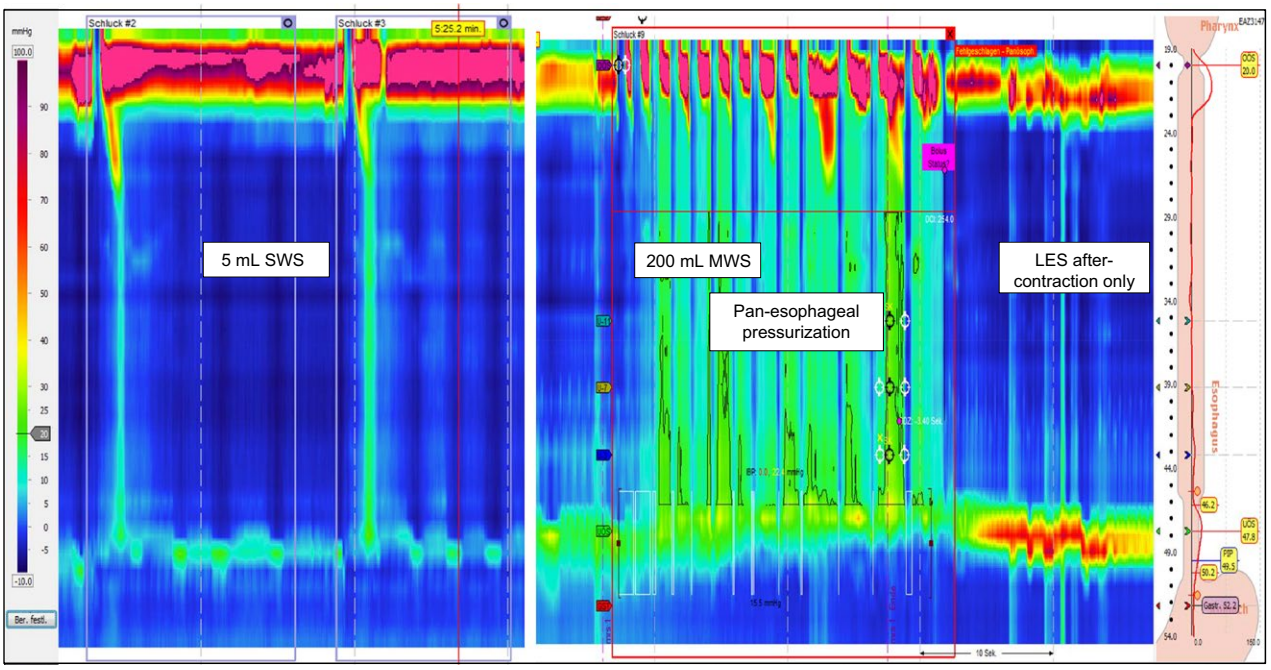

FIGURE 2 A 33-year-old man with dysphagia for solids and liquids. Manometry showed aperistalsis and a low LES (lower esophageal sphincter) pressure. Esophagogastric junction (EGJ) function documented by integrated relaxation pressure (IRP) was normal (8.6 mmHg) for single water swallows (SWS). With Rapid Drink Challenge (RDC), IRP-RDC increased to 15.5 mmHg and pan-esophageal pressurization >30 mmHg was present. These findings revealed impaired EGJ relaxation and/or opening (i.e., functional or structural EGJ obstruction). The final diagnosis was achalasia

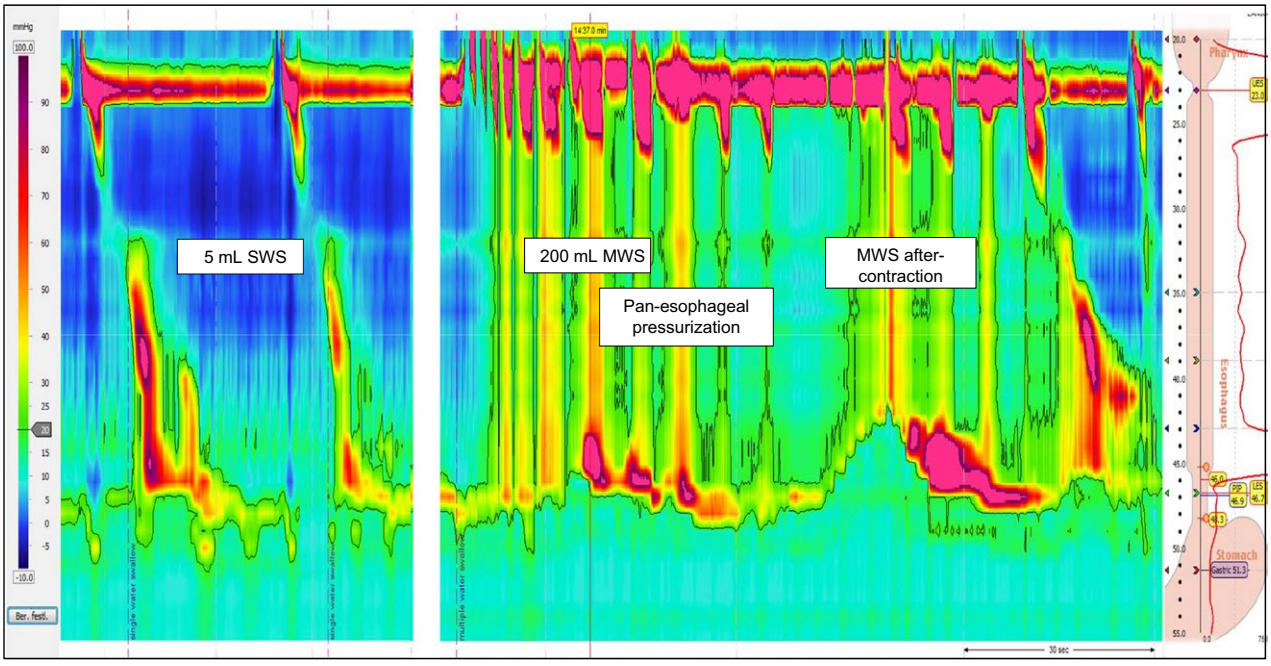

FIGURE 3 A 65-year-old male with persistent dysphagia primarily for solids. Endoscopy was normal. Barium swallow showed impaired bolus transport. Single water swallows (SWS) were subjectively abnormal but showed normal integrated relaxation pressure (IRP 10.8 mmHg) and distal latency (DL 5.3 s). During Rapid Drink Challenge (RDC), there was pan-esophageal pressurization (PEP) and compartmentalized pressurization during the after contraction (IRP-RDC 16.6 mmHg). This is evidence of outflow obstruction. Repeat endoscopy with biopsy revealed eosinophilic esophagitis as a cause of a poorly compliant LES in this patient

diagnostic thresholds were identified in a development set of patients and prospectively validated in an independent cohort with the full spectrum of esophageal motility disorders.

Rapid Drink Challenge data were acquired in a large number of HV (n=95) and also patient controls with esophageal symptoms but a normal manometry and normal 24-hour pH study (n=44). There were

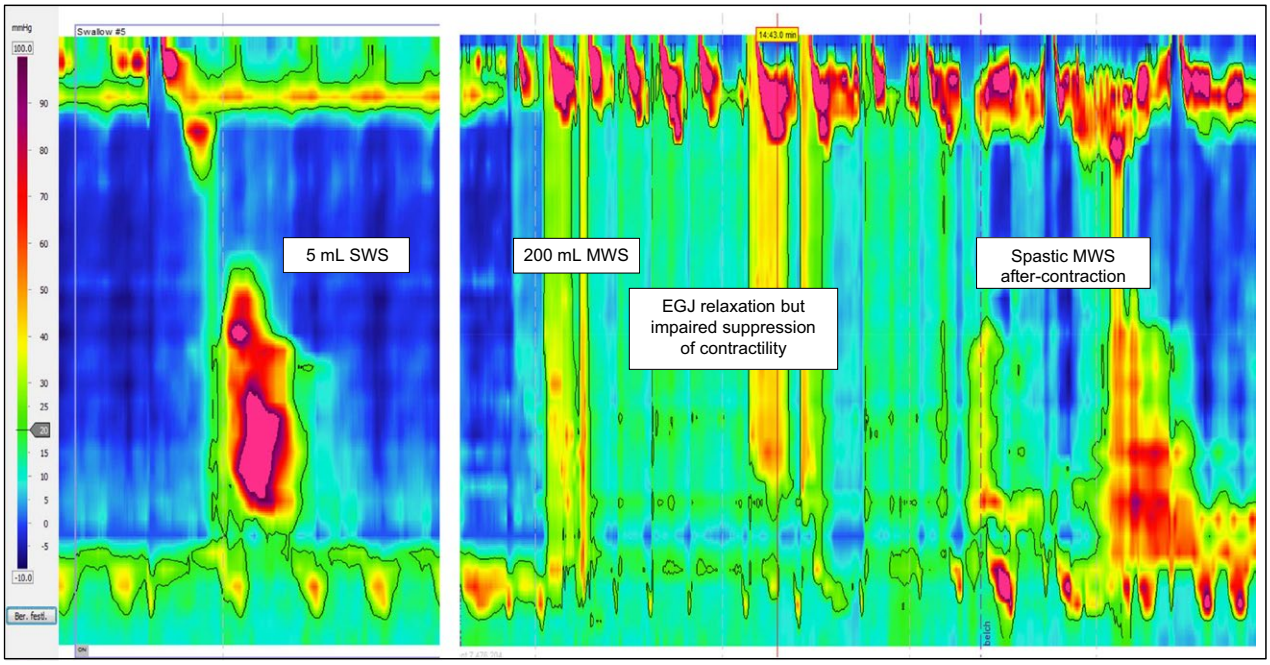

FIGURE 4 An 82-year-old male with dysphagia on drinking and eating. He also experienced heartburn and regurgitation. Single water swallows show esophageal spasm (distal latency 3.8 s) with borderline EGJ function (IRP 11.5 mmHg). Rapid Drink Challenge (RDC) shows failure of deglutitive inhibition with spastic after-contraction; however, EGJ relaxation is present with IRP within normal range (IRP-RDC 0 mmHg). Manometric features were considered to be more consistent with esophageal spasm than achalasia type III

A **Achalasia only**

IRP	15	12	11	10	9	8	7	6	5
Sens	0.86	**0.86**	0.86	0.86	0.86	0.86	0.93	0.93	0.93
Spec	1.00	**0.99**	0.99	0.98	0.97	0.95	0.92	0.89	0.85
PPV	0.92	**0.80**	0.75	0.71	0.60	0.46	0.36	0.29	0.24
NPV	0.99	**0.99**	0.99	0.99	0.99	0.99	0.99	0.99	1.00

B **All cause EGJ dysfunction (achalasia and EGJ outlet obstruction)**

IRP	15	12	11	10	9	8	7	6	5
Sens	0.78	0.78	0.78	0.78	0.78	**0.83**	0.89	0.89	0.89
Spec	1.00	0.99	0.99	0.98	0.97	**0.96**	0.93	0.90	0.86
PPV	0.93	0.82	0.78	0.74	0.64	**0.58**	0.44	0.36	0.29
NPV	0.99	0.99	0.99	0.99	0.99	**0.99**	0.99	0.99	0.99

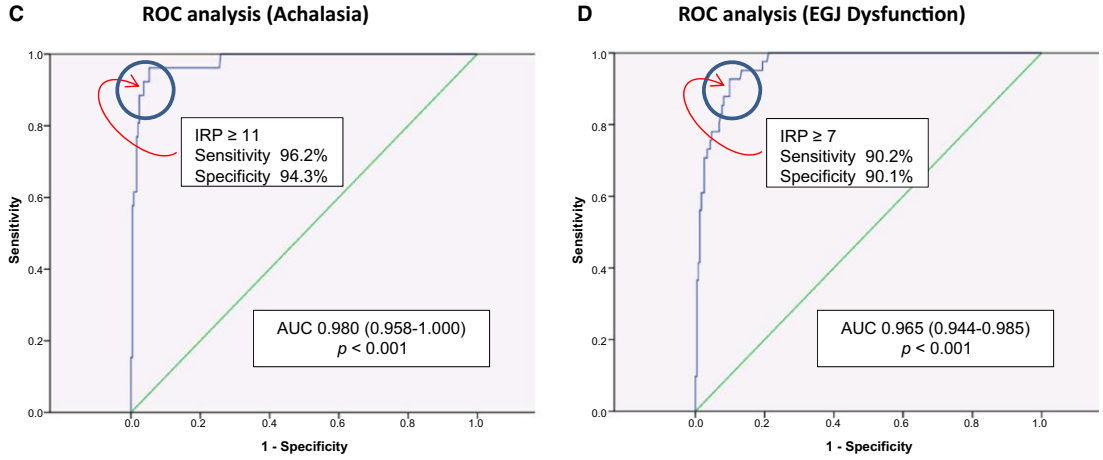

FIGURE 5 Diagnostic thresholds for IRP in the development set were in the range 10–12 mmHg for achalasia (A) and 6–8 mmHg for "all cause" EGJ dysfunction (B). Diagnostic accuracy of these estimates for diagnosis of achalasia and "all cause" EGJ dysfunction were tested in the prospective validation. The optimal diagnostic thresholds selected for achalasia (≥12 mmHg) and "all cause" EGJ dysfunction (≥8 mmHg) are highlighted. Receiver operating curve (ROC) analysis based on the development set was used to identify optimal diagnostic thresholds for achalasia (C) and "all cause" EGJ dysfunction (D)

no significant differences between these two control groups; however, inclusion of "patient controls" ensured that reference values were more representative of the patient population. Standard HRM metrics assessed esophageal inhibition using the IRP-tool during RDC and esophageal contractility after RDC. In the control groups, the upper limit of normal (99% CI) for IRP was lower during RDC than SWS in the upright position and much lower than normal values for SWS in the supine position (3 vs 5 vs 15 mmHg, respectively). These findings reflect complete relaxation and opening of the EGJ during free drinking in the upright position plus the reduction in mechanical work required to transport water into the stomach against intra-abdominal pressure.[17,20] This finding may also reflect the inhibitory effect of esophageal stretch receptors on EGJ function.[21] In almost all control patients there was profound inhibition also of peristaltic contractility during RDC. Subsequently, having finished the drink, the after-contraction was less vigorous following RDC than contractions associated with SWS. Indeed, only half of the healthy and patient controls demonstrated effective peristaltic contractions after the RDC and the average DCI of this after-contraction was significantly less than the average DCI from SWS. Overall, these observations are similar to those from Marin and Serra[13] and other case series,[11,18] but contrast with reports of increased contractile vigor after MRS.[15,16] The key difference between RDC and MRS is the volume of liquid ingested and the number of swallows taken. The MRS uses a small volume of water (total <10 mL) taken in five to six swallows. During RDC, a larger volume (typically 200 ml) is ingested rapidly at a rate determined by the patient. As a consequence, compared to MRS, RDC would be expected to be more sensitive to EGJ dysfunction because in such cases filling the esophagus with fluid increases intra-bolus pressure and the integrated relaxation pressure highlights functional or structural obstruction to bolus passage. Conversely, the after-contraction after RDC may be inhibited by repeated swallowing or activation of stretch receptors.[21] In short, the results of HRM measurements during MRS and RDC should not necessarily be considered equivalent. Each may provide complementary information.

Diagnostic thresholds were based on values established for SWS, normal and pathological values for RDC in the development set (Tables 4 and 5). Receiver operating characteristic analysis was utilized to establish normal and clinically relevant pathological values for EGJ and peristaltic function (Fig. 5). Optimal diagnostic thresholds were identified and prospectively validated in an independent patient cohort. Characteristic RDC findings in patients with a full range of esophageal motility disorders are described, including those with outlet obstruction (excluded by Marin and Serra). Overall, similar to controls, most patients showed very low IRP-RDC during RDC consistent with complete EGJ relaxation/opening and also complete suppression of contractility during RDC (Fig. 1). In contrast, results for the after-contraction in patients were highly variable.

Patients with Type I or II achalasia were the only group in whom IRP-RDC was unchanged or increased during RDC compared to SWS. For achalasia type III, IRP-RDC decreased but remained above the normal range. Additionally, in the vast majority of achalasia cases, PEP was observed due to rapid filling of the esophagus (Fig. 2). Analysis of the validation set identified IRP-RDC >12 mmHg during RDC as the optimal diagnostic threshold for diagnosis of achalasia. The threshold for "all cause" EGJ dysfunction at IRP-RDC >8 mmHg had 100% sensitivity for this diagnosis (Fig. 5). Three patients (3/34, 9%) with aperistalsis and one patient with esophageal spasm (1/17, 6%) based on the Chicago Classification version 3.0 had normal IRP-RDC during SWS but pathological IRP-RDC >12 mmHg during RDC. The final diagnosis in three cases was achalasia type I with low resting EGJ pressure and normal IRP-RDC during SWS. The final case had chronic EGJ outflow obstruction. In all cases EGJ dysfunction was revealed only when esophageal function was challenged by drinking a larger volume of water.

Most patients with EGJ outlet obstruction had lower IRP during RDC than SWS; however, this metric almost always remained above the upper limit of normal in controls. This observation indicates that for patients with a poorly compliant LES (e.g., due to inflammation) the large water load opens the sphincter, reduces IRP-RDC and facilitates bolus passage into the stomach. Notwithstanding the above, resistance to bolus passage was much higher in these patients compared to controls. Analysis of the validation set identified IRP-RDC >8 mmHg during RDC as the optimal diagnostic threshold for "all cause" EGJ dysfunction. This threshold identified all but one case of EGJ outlet obstruction diagnosed by SWS (likely false positive in an adipose patient). Moreover, RDC provided evidence of symptomatic outlet obstruction with IRP-RDC >8 mmHg in six additional cases that had normal or ineffective motility on SWS. These findings add to the evidence that RDC can detect occult outlet obstruction in patients with normal endoscopy, imaging, and manometry.[1,8,11] The inclusion of solids may further improve yield.[1,8,11]

Two of 17 (12%) patients with spasm or hypercontractile ("jackhammer") esophagus on SWS had elevated IRP-RDC >8 mmHg during RDC indicating EGJ obstruction. In some cases this represents achalasia type III, in others, muscle hyperplasia with impaired LES compliance.[22] In the development set, failure of deglutitive inhibition to suppress contractions during RDC was observed in nearly two-thirds of these patients, but was very rare in other patient groups (11/17 [65%] vs 5/126 [2%], $P<.0001$). The validation set showed failure of deglutitive inhibition during RDC in only 30% of patients with spasm or hypercontractile disorder. Thus, the presence of persistent contractions during or abnormal contractions after RDC is a specific marker of these conditions.

Considering patients with IEM during SWS, approximately half had an effective RDC after-contraction in the development and validation sets. The presence of an after-contraction in such patients may reflect "functional reserve" and has been linked to good outcomes after fundoplication in MRS studies.[15,23] Conversely, the absence of an effective RDC after-contraction in GERD patients has been linked to impaired clearance function and the presence of reflux esophagitis.[16] Although these findings are of interest, the lack of reproducibility for RDC after-contraction in IEM patients and controls should be considered when interpreting these results. It should be noted that poor reproducibility has been documented also for the MRS after contraction.[24] Further comparison of controls and patient data demonstrated

that an abnormal RDC after-contraction was a fairly sensitive but very non-specific marker of major and minor motility disorders (Table 3).

Patient reports of symptoms in association with abnormal esophageal function provides strong support for the clinical relevance of HRM findings.[25] Indeed the lack of symptoms induced during SWS may be a key limitation in current clinical studies. As expected, more patients were symptomatic during RDC compared with SWS. About one in three experienced dysphagia, pain, or regurgitation during or immediately after RDC, compared to <1 in 20 during SWS. The association between PEP, spasm, and symptoms provides a direct explanation for patient complaints and, in many cases, can direct specific and effective management.[1,8,11]

This study had limitations. In the absence of an independent reference standard, it is not possible to assess whether RDC improves diagnostic yield. Additionally, HRM metrics validated for SWS were applied to assess RDC; however, the biophysical principles that underpin these metrics are applicable in both cases. The advantage of using established metrics is the rapid implementation of RDC in clinical practice. The disadvantage is that certain metrics, specifically distal latency, can be difficult to assess due to repeated swallowing. On this basis the diagnosis of spasm for the RDC should include rapid contractile front velocity (>8 cm/s).[26] Behavioral factors can also be an issue. Healthy volunteers needed between 5 and 27 swallows to drink 200 mL water. In theory if the speed of ingestion exceeds the rate of esophageal emptying then this would elevate intra-bolus pressure and IRP-RDC. Conversely, drinking slowly can result in incomplete suppression of contractility if the time between swallows is longer than the period of deglutitive inhibition. The use of a straw prevents patients "gulping" the drink and setting time constraints (10–20 seconds) may improve data consistency.

In conclusion, RDC is a simple, quick, and essentially cost-free test that provides a "real-life" assessment of the esophageal swallow. Using objective HRM metrics from the Chicago Classification, this study establishes normal values and diagnostic thresholds for esophageal motility disorders. Initial data suggest that this adjunctive test can increase sensitivity for clinically relevant, symptomatic EGJ dysfunction. With few barriers to implementation, we consider that these data provide strong evidence for inclusion of RDC in routine clinical studies.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

DA performed data analysis, data interpretation, and drafted the manuscript; MF, BM, and RS developed the study concept and protocol, and were involved in data analysis, data interpretation, and writing the manuscript; MH, KK, JW, and ET acquired clinical data. All authors critically appraised the manuscript.

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